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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,849	02/07/2002	John Lyons	12636-260	1393

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EXAMINER	
KHARE, DEVESH	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,849	LYONS, JOHN	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/23/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43,44 and 46-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43,44 and 46-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's Amendment and remarks filed on 12/23/03 are acknowledged.

Claims 43 and 44 have been amended. Claims 1-42,45 and 52-58 have been cancelled without prejudice in the amendment to the claims. Claims 43-44 and 46-51 are currently pending in this application.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 43-44 and 46-51 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Von Hoff et al. (Ann. Int. Med. 85(2) pages 237-45, 1976) in view of Kantarjian et al. (Conference: Blood 98 (11), Part 1, pp 141a, 2001) of record.

Claims **43-44 and 46-51** are drawn to method for treating a patient having chronic myelogenous leukemia (CML), with a composition comprising a therapeutically effective amount of a DNA methylation inhibitor at a dose from 1 to 100 mg/m^2 per day in combination with imatinib mesylate.

Additional claim limitations include more than 30% blasts in peripheral blood or bone marrow where the patient's CML is staged, DNA methylation inhibitor is a cytidine analog or decitabine (5-azacytidine), administration by intravenous infusion at a dose ranging between 1 to 100 mg/m^2.

Von Hoff et al. teach the use and effectiveness of 5-azacytidine, the cytidine analog, in the treatment of acute myelogenous leukemeia (abstract). Von Hoff et al. discloses the effectiveness of 5-azacytidine in childhood leukemia or during the induction phase (page 239, col. 2nd. under European Trials). It is noted that Von Hoff et al. do not provide specific disclosure where the patient's CML is staged prior to administration or the administration is performed when the patient is in blast phase of CML, however Von Hoff et al. disclose that "5-azacytidine seems to be cell-cycle phase specific in that it is most toxic to cells in the S phase, especially at low concentrations" (page 238, first para.). It is also noted that both 5-azacytidine and decitabine which is 5-aza-2'-deoxycytidine (claim 48) have nitrogen in place of the fifth carbon in the base moiety (Von Hoff et al., page 237, 2nd para.). Von Hoff et al. teach the administration of 5-azacytidine by intravenous and subcutaneous routes (page 239, first col. first para. lines 2-7). Von Hoff et al. also suggest the dosage of 5-azacytidine for intravenous administration in the ranges of 1.1- 633.0 mg/m^2 (page 239, table 1 and page 240, 2nd col. 2nd para.). Von Hoff et al. disclose the doses from 2 mg/m^2 –3.3 mg/m^2 per day and can be increased to 70 to 100 times the initial starting dose (pages 239, last para. through page 240, first para.). Von Hoff et al. further teach the combination therapy of acute myelogenous leukemia with 5-azacytidine with other agents (page 241, table 3). Von Hoff et al. suggest a need for future clinical studies for using 5-azacytidine alone and in combination with other agents in the treatment of acute myelogenous leukemia (page 244, first col. third. para.).Von Hoff et al. differs from the applicant's invention that

Von Hoff et al. do not provide an example of the administration of the pharmaceutical composition, comprising 5-azacytidine in combination with imatinib mesylate.

Kantarjian et al. teach the treatment of CML with imatinib mesylate (see abstract). Kantarjian et al. disclose the treatment of patients with CML with imatinib mesylate 400-600 mg/day (lines 1-2) for blasts 10-14% (lines 5-6). Kantarjian et al. also suggest a need for future clinical studies in CML treatment with imatinib mesylate in combination with decitabine (5-aza-2'-deoxycytidine) (see last two lines).

Therefore, one of ordinary skill in the art would have found the applicants claimed method for treating a patient having chronic myelogenous leukemia (CML), with a therapeutically effective amount of a 5-azacytidine (an analog of cytidine or a DNA methylation inhibitor) in combination with imatinib mesylate, to have been obvious at the time the invention was made having the above cited references before him. Since Von Hoff et al. teach the use and effectiveness of 5-azacytidine, in the treatment of acute myelogenous leukemeia, and Kantarjian et al. teach the treatment of CML with imatinib mesylate, one skilled in the art would have a reasonable expectation for success in combining the teachings of these references to accomplish the treatment of CML because both 5-azacytidine and imatinib mesylate have shown activity against resistant phase CML as single agents and were therefore tested in combination. The motivation for doing so is provided in the prior art, Kantarjian et al. suggest a need for future clinical studies in CML treatment with imatinib mesylate in combination with decitabine (5-azacytidine) (see last two lines).

Rejection Maintained

Rejections of claims 43-44 and 46-51 under 35 U.S.C. 103(a) are maintained for the reasons of record.

Response to Arguments

Applicant's arguments traversing the rejection of claims 43-44 and 46-51 under 35 U.S.C. 103(a) have been fully considered but they are not persuasive.

Applicants argue that "Neither van Hoff et al. nor Kantarjian et al. teach or suggest the claimed method of treating a patient in blast phase of CML with a DNA methylation inhibitor (e.g, decitabine) at a dose ranging from 1to 100 mg/m^2 per day in combination with imatinib mesylate". Von Hoff et al. teach the use and effectiveness of 5-azacytidine, the cytidine analog, in the treatment of acute myelogenous leukemeia (abstract). It is noted that Von Hoff et al. do not provide specific disclosure where the patient's CML is staged prior to administration or the administration is performed when the patient is in blast phase of CML, however Von Hoff et al. disclose that "5-azacytidine seems to be cell-cycle phase specific in that it is most toxic to cells in the S phase, especially at low concentrations" (page 238, first para.). It is also noted that the anticancer activity of both 5-azacytidine and decitabine which is 5-aza-2'-deoxycytidine (claim 48) is due to the nitrogen in place of the fifth carbon in the base moiety (Von Hoff et al., page 237, 2nd para.). Von Hoff et al. also disclose the doses from 2 mg/m^2 –3.3 mg/m^2 per day and can be increased to 70 to 100 times the initial starting dose (pages

239, last para. through page 240, first para.). Furthermore, Kantarjian et al. disclose the treatment of patients with CML with imatinib mesylate 400-600 mg/day (lines 1-2) for blasts 10-14% (lines 5-6). Indeed, the examiner has established a prima facie case of obviousness rendering claims 43-44 and 46-51 rejected under 35 U.S.C. 103(a) by addressing sufficiently all of the limitations set forth in the instant claims, one skilled in the art would have a reasonable expectation for success in combining the above said references to accomplish a method for treating a patient having chronic myelogenous leukemia (CML), with a composition comprising a therapeutically effective amount of a DNA methylation inhibitor at a dose from 1 to 100 mg/m^2 per day in combination with imatinib mesylate.

2. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the

Examiner should be directed to Devesh Khare whose telephone number is 571-272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Supervisory Patent Examiner, Art Unit 1623 can be reached at 571-272-0661. The official fax phone numbers for the organization where this application or proceeding is assigned is (703) 308-4556 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Devesh Khare, Ph.D.,J.D.
Art Unit 1623
May 24,2004

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600